

INTERNATIONAL
POSITION PAPER

on

**WOMEN'S HEALTH
AND MENOPAUSE:
A COMPREHENSIVE
APPROACH**

*NATIONAL HEART, LUNG,
AND BLOOD INSTITUTE*

*OFFICE OF RESEARCH ON
WOMEN'S HEALTH*

NATIONAL INSTITUTES OF HEALTH

AND

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PREFACE

Women's health and menopause is a rapidly expanding field of medical practice and scientific investigation. It is a field of great social importance and impact, nationally and globally, in developed as well as developing countries.

Menopause is a normal event in a woman's life. Some women view it as a positive and liberating experience. Others think of it as a negative event. Today, most women live long enough to become postmenopausal. In the developed world, the percentage of women over 50 years of age has tripled in the last 100 years. During this period, women's life expectancy in the United States has increased from 50 to 81.7 years, meaning that more than one third of life will be lived in postmenopause.

This "International Position Paper on Women's Health and Menopause: A Comprehensive Approach" is based on extensive international review and evaluation of the scientific evidence for current clinical practices as presented in the published literature. The purpose of this international and multidisciplinary monograph is to enhance the composite health of menopausal and postmenopausal women on a global basis, with consideration of sociocultural concerns and economic issues.

The monograph represents the culmination of 7 years of cooperation between the National Heart, Lung, and Blood Institute (NHLBI) and the Giovanni Lorenzini Medical Science Foundation (Milan, Italy and Houston, TX) in a public/private partnership in the development and cosponsorship of four international conferences on Women's Health and Menopause since the mid-1990s. The first three

conferences were held in Italy, and the most recent one was held in May 2001 in Washington, DC. The last two conferences were also cosponsored by the Office of Research on Women's Health (ORWH), National Institutes of Health (NIH). These conferences have addressed not only cardiovascular disease, but also other health problems, such as cancer, osteoporosis, and Alzheimer's disease, as well as the use and impact of hormone replacement therapy.

Menopause offers the primary care health provider an opportunity to assess a woman's health, her concerns, and her needs for health promotion and disease prevention measures worldwide. Given the multifactorial approaches needed for women during their middle and older years, the NHLBI, the ORWH, and the Giovanni Lorenzini Medical Science Foundation, in a cooperative venture assembled an international panel of experts on menopausal health.

The individual chapters of the International Position Paper, prepared by panel members and invited authors, evaluate published research studies to establish relevant background information and compile strategies for management. These were reviewed by internationally acknowledged leaders in their fields. The volume describes and references relevant clinical information and provides evidence-based recommendations for best clinical practices as well as recommendations for future research. Importantly, the goal of this monograph is that the materials be reproduced and translated in individual countries for optimal global dissemination, which will be furthered by presentations at topic-related scientific meetings.

On behalf of the NHLBI, I would like to thank Nanette K. Wenger, M.D., chair of the Executive Committee of the International Position Paper; Rodolfo Paoletti, M.D., cochair; Vivian W. Pinn, M.D., cochair; the panel members; the nonpanel coauthors; and the experts who reviewed the preliminary versions of the individual chapters and of the composite document for their valuable scientific contributions and dedication during this 4-year effort to critically review and evaluate extensive international databases on women's health and menopause. I hope that the readers will come away with a sense of appreciation for what biomedical research has accomplished in this important field and anticipation of the many opportunities and needs for future research.

A handwritten signature in dark ink, appearing to read "C. Lenfant", with a stylized, flowing script.

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CHAPTER 1: EXECUTIVE SUMMARY

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1. INTRODUCTION

Today, most women live long enough to become menopausal. In the developed world, the percentage of women over 50 years of age has tripled in the last 100 years. Mean female life expectancy has increased from 50 to 81.7 years, meaning that more than one-third of life will be lived in postmenopause. The absolute and relative numbers of older people in both developed and developing countries substantially increased during the 20th century, and the mean age of the population of the world will increase much faster in the next half century. It is projected that there will be almost 2 billion (1,970 million) older persons in 2050, compared with 580 million in 1998; the majority of these elderly are women. The quality of life of older women in the aging population will depend in large measure on the ability of societies to cope with the economic, social, and medical challenges of the postmenopausal years.

Menopause is not a disease, but rather a normal physiologic event in a woman's life. It can be associated, however, with health complaints, a decrease in quality of life, and an increase in risk for illnesses,

such as osteoporosis and coronary heart disease (CHD). Studies of menopause are numerous but largely recent. Although many clinically relevant questions remain unanswered, women seeking

advice about menopause currently have more options and better interventions for healthy menopausal years than ever before. Menopause is a time in a woman's life when the primary health care provider should assess a woman's health and her need for health promotion and disease prevention measures.

Given the multifactorial approaches needed for women during their middle and older years, the National Heart, Lung, and Blood Institute (NHLBI) and the Office of Research on Women's Health of the National Institutes of Health (NIH) in Bethesda, MD and the Giovanni Lorenzini Medical Science Foundation of Milan, Italy, and Houston, TX, in a cooperative venture assembled

Menopause is a time in a woman's life when the primary health care provider should assess a woman's health and her need for health promotion and disease prevention measures.

an international panel of experts on menopausal and postmenopausal health. Through a collaboration that included a series of meetings from November 1998 to July 2000, the Executive Committee and Panel members evaluated published information to determine management strategies that would constitute evidence-based recommendations on menopause for best clinical practice. Evidence statements and recommendations were categorized by a level of evidence ranging from A to D as shown in table 1–1 and indicated within square brackets in the text. Additional participants in document development were referees and reviewers, selected by the Executive Committee in cooperation with the panel members. The resulting multichapter monograph addresses a spectrum of evidence to provide a multidisciplinary approach to the enhancement of menopausal and postmenopausal health globally. Although the evidence reviewed is disease specific, the monograph is designed to enhance the composite health of menopausal and postmenopausal women and is not intended to medicalize menopause.

Menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity.

The terms “*estrogen replacement therapy (ERT)*” and “*hormone replacement therapy (HRT)*,” along with their initialisms ERT and HRT, are well established; nevertheless, the panel concurs with critics who view *replacement* as suggesting that menopause is a disease state and that hormonal status should be restored to that of the reproductive years.

In the absence of scientific consensus regarding a more appropriate term, the panel has decided to use the term HRT for the present monograph, since HRT is now the most common in use by the medical profession and familiar to the general public. Possible benefits and risks of HRT are summarized in table 1–2.

2. MENOPAUSE AND AGING

- Menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhea for which there is no other obvious pathologic or physiologic cause. At present, it can be recognized only retrospectively.
- Endocrine changes will have begun years earlier. Changes in serum concentrations of follicle-stimulating hormone (FSH) and estradiol are maximal in the year of the final menstrual period (FMP). FSH elevation, while a harbinger of menopause, is a poor predictor of age at menopause; the clinician cannot draw any conclusions about the timing of an individual woman’s menopause on the basis of the presence or degree of FSH elevation.
- The endocrine changes of menopause do not include any acute decrease in androgens. After menopause, estrone, rather than the more potent estradiol, is the major circulating estrogen. It is produced primarily by peripheral aromatization of androgens, so that fat cells become the major source of endogenous estrogen after menopause.
- There is considerable individual and racial/ethnic variation in age at natural menopause, in climacteric signs and symptoms, and in what may be considered menopause-related sequelae.
- There is a lack of consensus as to whether changes in health occurring during the climacteric or presenting later in life are attributable to menopause and reduced ovarian function or to aging.

TABLE 1–1**Evidence Categories**

Evidence Category	Sources of Evidence	Definition
A	Randomized, controlled trials (rich body of data)	Evidence is from endpoints of well-defined RCTs (or trials that depart only minimally from randomization) that provide a consistent pattern of findings in the population for which the recommendation is made. Category A, therefore, requires substantial numbers of studies involving substantial numbers of participants.
B	Randomized, controlled trials (limited body of data)	Evidence is from endpoints of intervention studies that include only a limited number of RCTs, post hoc or subgroup analysis of RCTs or meta-analysis of RCTs, controlled trials. In general, category B pertains when few randomized trials exist, they are small in size, and the trial results are somewhat inconsistent, or the trials were undertaken in a population that differs from the target population of the recommendation.
C	Nonrandomized trials and/or observational studies	Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.
D	Expert judgment	Expert judgment is based on the authors' synthesis of evidence from research described in the literature that does not meet the above-listed criteria, taking into consideration critical advice by other members of the international panel of experts, external referees, and external reviewers. The category is used only in cases in which the provision of some guidance was deemed valuable but an adequately compelling clinical literature addressing the subject of the recommendation was deemed insufficient to justify placement in one of the other categories (A through C).

Source: Adapted from the NIH. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The Evidence Report*. Bethesda, MD, 1998; NIH publication no. 98–4083.

TABLE 1–2

**Possible Benefits and Risks of Hormone Replacement Therapy,
With Evidence Categories**

	<i>Regimen</i>	
	Estrogen Alone	Estrogen Plus Progestin
<i>Possible Benefits</i>		
Hot flushes	Significant reductions [A]	Same [A]
Symptoms of vulvovaginal atrophy	Improvements, with topical as well as systemic administration [A/C]	Improvements with systemic preparation (only available preparation) [A/C]
Decreased sexual function*	Variable success; data inconclusive [B]	Estrogen and androgen: same [B]
Urinary flow problems	Alleviation in many cases of urgency, urge incontinence, frequency [B], nocturia, and dysuria [D]; may worsen genuine stress incontinence [A]	Same
Urinary tract infection	Reduction in frequency, with local as well as systemic administration [D]	Same [D]
Osteoporosis	Maintenance of bone density and favorable effects on markers of bone resorption [A]; marked reduction in risk for vertebral fracture [B]; non-vertebral fracture [C]	Same
Oral bone loss*	Possible benefit [C/D]	Same [C/D]

Note: Evidence categories are shown in square brackets. A = randomized clinical trials (rich body of data); B = randomized clinical trials (limited data); C = nonrandomized trials and observational epidemiologic studies; D = Panel expert judgment. (See also table 1–1.)

* Because clinical data are sparse or inconclusive, consideration of potential benefit would ordinarily be overridden by the extent to which benefits and risks of HRT are well characterized for other organ systems or disorders.

† All findings belong to evidence category C, as they address side effects rather than interventions. This should not weaken the significance of the results.

TABLE 1–2 (continued)

	Regimen	
	Estrogen Alone	Estrogen Plus Progestin
Possible Benefits		
Neurologic function and mental health*	Possible preservation of certain cognitive skills during the period immediately after induced menopause [B] and during the aging process [C]; possible reduction in risk for Alzheimer's disease with replacement therapy begun after menopause [C], with no effect when begun after the onset of dementia symptoms [B]; possible benefit in certain sleep disorders occurring during the climacteric [C]; possible positive effect on mood [B]	Possible preservation of certain cognitive skills during the aging process [C]; possible reduction in risk for Alzheimer's disease with therapy begun after menopause [C]; possible benefit in certain sleep disorders occurring during the climacteric [C]; possible positive effect on mood [C]
Eye*	Little evidence of an effect on age-related maculopathy, cataract, and dry eye [C]	Same [C]
Colorectal cancer*†	Possible reduction in risk	Same, but less information available
Possible Risks		
Period-like symptoms, including vaginal bleeding	Vaginal bleeding may occur [A]	May improve, remain the same, or worsen depending on the specific formulation (e.g., MPA versus norethindrone acetate), dose, or schedule (sequential versus combined continuous) of the progestin [A]
Mastalgia	Significant increase in breast tenderness [A]	Same or increased discomfort [A]
CHD events	Apparent increase in risk in the first 1 or 2 years of therapy [A]; no definitive evidence-based rationale to recommend for prevention of disease	Same
Stroke	Conflicting results; no overall effect on stroke risk [B] or possible increase in risk and possible decrease in stroke mortality [C]	Same

TABLE 1–2 (continued)

	Regimen	
	Estrogen Alone	Estrogen Plus Progestin
Possible Risks		
Venous thromboembolic events in legs and lungs	Increase in risk, perhaps fourfold increase in RR initially, with a persistent twofold increase thereafter [A]	Similar [A]
Breast cancer*†	No appreciable risk association with short-term (< 5 years') use; moderate excess risk with longer use for current users but not for former users	Possible higher risk compared with unopposed estrogen
Endometrial cancer*†	Significant increase in risk	Not related to a major excess risk when progestins are given for more than 10–14 days per cycle
Ovarian cancer*†	Possible increase in risk	No adequate information
Gallbladder disease	Apparent increase in risk [B/C]	Apparent increase in risk [B/C]
Asthma	Possible increase in risk with CEEs [C]	No data

- Estimates of the median age of menopause range from 45 to 55 years worldwide. Understanding of the factors that influence age at menopause is limited. Familial or hereditary factors appear to be the most predictive. Of other variables studied, the most consistent relation is for cigarette smoking, which advances menopause by 1 to 2 years. The timing of menopause may substantially influence subsequent morbidity and mortality.
- Contraception is still needed during the menopausal transition.

3. SYMPTOMS AND THE MENOPAUSE

- The climacteric* is sometimes but not always associated with symptoms. There is debate as to whether the term “*symptoms*” should be used when referring to events of the climacteric. The term is used here to refer to those bodily perceptions presented as complaints by the individual woman. The presence of occasional symptoms does not indicate their impact on the woman and may not be clinically relevant or indicative of treatment needs.
- Conflicting findings as to the causes of symptoms in midlife reflect some of the methodologic difficulties inherent in menopause research as well as specific issues pertaining to the measurement of symptoms. General methodologic issues relate to sample selection, validity of

symptom measures, cultural factors, determination of menopausal phase, lack of systematic hormonal level assessment, age at baseline and length of followup, separation of the effects of natural menopause transition from those of induced menopause, and statistical and experimental design. A number of studies suggests that symptom experience is likely to be worse when women have undergone surgical menopause. There is a risk that stereotypes will become operative in menopause research when subjects know the topic of the research.

- Individual women may view menopause as negative and troublesome or positive and liberating. Importantly, the knowledge base on menopause is narrow in that most studies have been carried out on white women of northern European ancestry; relatively little is known about the range of climacteric experiences in women of other racial/ethnic groups. Only studies of women derived randomly from a general population provide findings that can be confidently generalized to be the experience of most women of that particular culture and geographic location.
- The following generalizations about climacteric symptoms can be made.
 - When symptom checklists are used, middle-aged women are highly symptomatic.
 - Age-related symptoms have to be differentiated from those related to the menopausal phase.
 - It is important to consider whether reported symptoms reflect a change relative to a baseline level.
 - Only vasomotor symptoms, vulvovaginal atrophic symptoms, and breast tenderness consistently vary with the phase of the climacteric and are significantly affected [A] by the administration of hormones.

- Other symptoms, such as insomnia and changes in mood, may be affected by the presence of bothersome vasomotor symptoms.
- Symptoms are influenced by psychosocial and lifestyle factors.

3.1 Vasomotor Symptoms

In North America and Europe, most women have at least some menopausal hot flushes (also called hot flashes). While menopausal hot flushes have been described in a limited number of studies in a variety of other cultures, the prevalence varies widely. There is consensus about the marked temporal relation of vasomotor symptoms to the climacteric. They begin to increase in the menopausal transition, peak 1 to 2 years after the FMP, and may remain increased for several years. A number of studies have shown a statistical relation between hot flushes and night sweats, and some show a relation between those vasomotor symptoms and insomnia. The mechanism of menopausal flushing remains unclear. Core body temperature elevations precede the menopausal hot flush and serve as one trigger of the heat loss phenomenon, but what is responsible for the core temperature elevation is uncertain.

The knowledge base on menopause is narrow in that most studies have been carried out on white women of northern European ancestry.

- ***Hormone replacement therapy.*** Estrogen therapy is effective in reducing hot flushes [A]. The use of continuous or sequential progestins with estrogen does not reduce the efficacy of estrogen in the reduction of hot flushes.
- ***Other pharmacologic agents.*** Other agents reported to be more effective than placebo in decreasing hot flushes include megestrol acetate, veralipride, opipramol, venlafaxine, sertraline, paroxetine, and tibolone [B].

* Perimenopause comprises the period of time immediately before menopause (when the endocrinologic, biologic, and clinical features of approaching menopause commence) and the first year after menopause. The climacteric incorporates perimenopause by extending for a longer, variable period of time before and after it.

- **Physical activity.** Evidence is conflicting as to whether increased physical activity affects menopausal symptoms.
- **Foods and beverages.** Avoidance of hot beverages, foods containing nitrites or sulfites, spicy foods, and alcohol may help limit hot flashes.
- **Phytoestrogens.** Although some evidence suggests that dietary supplementation with phytoestrogens yields improvements in hot flashes, the issue remains unclear because of methodologic limitations of the studies.

Estrogen therapy is effective in reducing hot flashes.

- **Gamma-linolenic acid.** Gamma-linolenic acid provided in evening primrose oil, a popular alternative therapy, appears to offer no benefit over placebo in the treatment of vasomotor symptoms [B].

3.2 Vulvovaginal Atrophic Symptoms

Atrophic changes of the vulva, vagina, and lower urinary tract are common causes of complaints among menopausal women. Only vulvovaginal atrophic changes can be clearly related to menopause; findings as to whether disorders of urinary tract atrophy are menopause or age related are conflicting. (See also “Lower Genital and Urinary Tract Atrophy” in “Gynecologic and Urinary Aspects” below.) With estrogen loss, the vagina shortens and narrows, and its walls become thinner. Decreased production of lactic and acetic acids alters the normal low vaginal pH, to create a milieu that does not favor continued growth of the normal flora. A decrease in estrogen-supported lubrication causes vaginal dryness, which can lead to vaginitis, vaginismus, and dyspareunia. Cystocele and rectocele are also common problems in postmenopausal women.

- **Hormone replacement therapy.** Estrogen therapy is effective in relieving vulvovaginal atrophic symptoms, and local estrogen preparations are as effective as systemic ones [A]. In observational studies, ERT reduces the frequency of urinary tract infections in the menopausal years [D].

3.3 Mastalgia (Breast Soreness/Tenderness)

In clinical trials, mastalgia has been related to estrogen and progestin concentrations [A]. Mastalgia that is related to the menstrual period often resolves with menopause. Compliance with HRT can be limited by the side effect of mastalgia.

4. SOCIOCULTURAL ISSUES

- Attitudes toward and beliefs about menopause vary historically and among cultures [C].
- Cross-cultural comparisons demonstrate that reported symptoms can vary significantly among countries and among ethnic groups within countries in type (e.g., vasomotor, psychologic) and in the degree of distress caused [C].
- Difficulties in integrating findings from cross-cultural studies stem from a number of limitations. Among these are differences among cultures in language used to describe symptoms, use of different methodologies in study design and in instruments used to measure symptoms, and differences in diet and other lifestyle factors that make it difficult to establish cultural versus biologic causes of symptom expression.
- A better appreciation of cross-cultural differences in the experience of menopause may derive from an emerging interdisciplinary model in which symptoms are seen as a result of increased vulnerability due to hormonal changes in interaction with psychologic and sociocultural factors.

5. PHYSIOLOGICAL ROLE OF ESTROGEN AND ESTROGEN RECEPTORS AND PHARMACOLOGIC MODULATION OF ESTROGEN RECEPTOR ACTIVITY

- The two known estrogen receptor (ER) subtypes, ER α and ER β , mediate many biologic effects of estrogens and antiestrogens.
- Different ligands induce different ER conformations.
- Different mechanisms of target gene regulation affect the agonist/antagonist profile of a ligand. Selective ER modulators (SERMs) have a tissue- and gene-specific mixed agonist/antagonist effect.
- Of interest are the SERMs (third-generation HRT), nonsteroidal agents that behave as agonists in target tissues such as bone and liver and as antagonists or partial agonists in reproductive tissues [A/B].
- Both subtypes are also important for normal ovarian follicular development and female fertility.
- Available data suggest that ER α plays an important role in bone maturation and homeostasis in both women and men, and that ER β has a specific role in bone physiology in women.
- ER α and ER β are expressed in vascular endothelial cells, vascular smooth muscle cells, and myocardial cells. Beneficial effects of estrogens on cardiovascular function and reactivity stem from direct effects on cells in the vascular system and also from effects on liver and on circulating monocytes/macrophages.
- In the central nervous system (CNS), estrogen is linked to a variety of functions, including learning, memory, awareness, fine motor skills, temperature regulation, mood, reproductive functions, and depression. The predominance of expression and localization of ER β in rat neocortex, hippocampus, and nuclei of the basal forebrain suggests an important role for ER β in learning and memory.
- Estrogen and inhibins produced by the ovaries are important feedback regulators of the hypothalamic-pituitary axis and serum concentrations of luteinizing hormone (LH) and FSH. ER α seems to be more involved than ER β in the LH, FSH feedback loop.
- Increased knowledge of the structure of ERs and of the mechanisms of the receptors' synthesis and their interaction with key elements of the transcription apparatus is facilitating the synthesis of new pharmacologically active molecules.
- ER α - and ER β -selective SERMs in development might provide improved therapy. Since both ER subtypes are expressed in human breast cancer, measurements of both ER α and ER β may help in the selection of appropriate breast cancer therapy.

5.1 Hormone Replacement Therapy and Related Therapies

The regimens most commonly used to treat climacteric symptoms and to intervene against menopausal and postmenopausal health risks are 17 β -estradiol, esterified estrogens, and conjugated equine estrogens (CEE) in combination with a progestin, for example, medroxyprogesterone acetate (MPA). The awareness of undesired effects and serious health risks (breast cancer, endometrial cancer, and venous thromboembolism) with existing HRT call for alternatives with improved safety profiles.

Alternative regimens for women who do not wish to take estrogen exist. Non-ER subtype-selective SERMs display tissue-selective estrogen agonism. They do not increase the risk of breast and endometrial cancer but aggravate hot flashes and increase the risk of venous thromboembolism. The existence of two ER subtypes provides the oppor-

The two known ER subtypes, ER α and ER β , mediate many biologic effects of estrogens and antiestrogens.

tunity to develop ER subtype-selective ligands; such agents will likely have improved therapeutic profiles. Novel synthetic steroidal ER agonists hold promise because of agonist activity for progesterone and androgen receptors.

Multiple population-based studies imply a decrease in female sexual function associated with the midlife years.

6. SEXUALITY

Multiple population-based studies imply a decrease in female sexual function associated with the midlife years, and there is growing evidence that the decrease reflects hormonal changes of the menopausal transition rather than increasing age. Hormonal

change is only one of many factors that affect sexual function. Other factors include presence of a sexual partner, partner's age and health, length of the relationship, feelings toward the partner, level of past sexual function, social class, educational level, experience of physical or psychologic ill health, stressors, employment, personality factors, and negative attitudes toward menopause.

- Declining sexual function is common but not universal with aging. There may be an additional decrement associated with the menopausal transition.
- The causes of decreased sexual activity are multiple and include physiologic, psychological, and social factors.
- Definitions and Classification of Female Sexual Dysfunction given by the consensus panel of the Sexual Function Health Council of the American Foundation for Urologic Disease provide a standardized system for clinical diagnosis and treatment and are recommended for use by health care professionals [D].

- Sexual interest, behavior, and activity should be routinely assessed at office visits on a regular basis, and a plan should be developed to address the woman's concerns.
- HRT (estrogen or estrogen plus androgen) and behavioral therapy have had variable success in the treatment of sexual dysfunction [B] but should be considered in patients who desire treatment.
 - **Hormone replacement therapy.** Although estrogen is effective in relieving vulvovaginal atrophic symptoms, including increasing vaginal lubrication, HRT has not been consistently shown to increase sexual desire or activity [B].

7. CARDIOVASCULAR AND PULMONARY DISEASE

- Cardiovascular disease (CVD) remains the commonest single cause of female mortality and morbidity in the western world [C]. Despite the protection apparently offered by endogenous sex hormones in their premenopausal years, the longevity of women exposes them to a lifetime risk for coronary and other vascular diseases similar to that of men. There is a wide variation in CHD incidence among countries. In countries in which the incidence is high in men, it is also high in women; likewise, the incidence is low in women and men in countries with low rates of CHD. Because CVD tends to develop at a later age in women than in men, women are more likely to have complicating comorbidities, such as hypertension and diabetes mellitus, which contribute to poorer short-term outcomes after coronary events or revascularization.

7.1 Coronary Heart Disease

- Major modifiable risk factors for atherosclerotic CHD are similar in women and men and include dyslipidemia, hypertension, diabetes mellitus, cigarette smoking, lack of physical activity, and obesity (especially abdominal obesity) [C].

The atherogenic risk profile of older women is appreciably more adverse than that of younger women, although it is uncertain whether age or hormone status is the primary determinant of the evolution of the adverse risk profile.

- Large randomized, placebo-controlled clinical trials have shown that beta-blockers, aspirin, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), and angiotensin-converting enzyme (ACE) inhibitors reduce risk for CHD events in women as well as in men [A]. For some of these therapies, the evidence derives largely from secondary prevention trials; in general, therapies that work in secondary prevention will work in primary prevention as well. Treatment effects appear to be similar in women and men. For example, meta-analysis of data from several major lipid-lowering statin trials showed a 29-percent reduction in risk for major CHD events in women, similar to the 31-percent reduction observed in men.
 - HRT has consistently been shown to improve the blood lipoprotein profile markedly, and many large observational studies found that menopausal women who chose to use hormone therapy had a 35- to 50-percent lower risk for CHD than nonusers. In contrast, no hormone benefit on hard cardiovascular outcomes, such as myocardial infarction (MI) or cardiac death, has been demonstrated in clinical trials [B]. In fact, there appears to be an excess risk for cardiovascular events in the first year or two of treatment [A], although coronary benefit over the long term remains possible [B].
- In the Heart and Estrogen/progestin Replacement Study (HERS), the first published large trial conducted in postmenopausal U.S. women with CHD, those assigned to daily oral CEE plus MPA had an increased relative risk (RR) versus placebo for nonfatal MI and coronary

death during the first year and did not have coronary benefit across the average followup of 4.1 years. Also, more women in the hormone replacement group experienced venous thromboembolic events and gallbladder disease [A].

- The large Women's Health Initiative (WHI) trial of HRT in the United States includes predominantly women without prior CVD and includes women treated with daily CEEs alone or daily CEEs with MPA, versus placebo. All WHI participants were informed of an increased risk associated with active treatment for heart attack and stroke, during the first 2 years after enrollment (www.nhlbi.nih.gov/whi/hrt-en.htm). The majority of participants did not have prior CVD, and the subgroup with prior disease did not account alone for these findings. The trial is continuing to assess long-term benefits and risks of HRT [B].

Major modifiable risk factors for atherosclerotic CHD are similar in women and men and include dyslipidemia, hypertension, diabetes mellitus, cigarette smoking, lack of physical activity, and obesity.

- In the angiographic Estrogen Replacement and Atherosclerosis (ERA) study, there was no coronary angiographic lesion benefit from either estrogen or estrogen plus progestin replacement therapy compared with placebo [A].
- Preliminary results from the PHASE trial of transdermal HRT for secondary prevention have not shown cardioprotective benefit to postmenopausal women taking estrogen or estrogen plus a progestin compared to the placebo group [B].¹

A lack of benefit may be due to countervailing adverse changes in coagulation or inflammatory mechanisms. In view of sex differences in atherosclerotic plaque and the vascular remodeling effects of estrogen and progesterone, other doses, preparations, or routes of administration may prove to have an important role in the prevention of CVD in women.

- **Hormone replacement therapy.** There is no definitive evidence-based rationale to recommend HRT for the prevention of CHD [A].

- At present, prevention of CHD should rely on identifying and treating the classic risk

factors, such as dyslipidemia, hypertension, diabetes mellitus, smoking, obesity, and sedentary lifestyle [A]. Vigilant management of risk for CHD in women is imperative.

- Instead of HRT, HMG-CoA reductase inhibitors (statins), beta-blockers, ACE inhibitors, and aspirin should be recommended to all eligible women with CHD or diabetes mellitus [A].

- **Phytoestrogens and selective estrogen receptor modulators.** There are insufficient data to make recommendations regarding the use of soy phytoestrogens or SERMs for prevention of CHD [C].

7.2 Stroke

Despite similar stroke rates, women are more likely than men to die of stroke. The main risk factors for stroke are not gender dependent. Although strokes are more closely related to hypertension (which is probably their most important risk

factor) than to hypercholesterolemia, HMG-CoA reductase inhibitors (statins) reduce risk for stroke, as do antihypertensive medications.

- **Hormone replacement therapy.** HRT has not been consistently linked to stroke protection. In the HERS trial of continuous CEEs combined with MPA in women with prior CHD, HRT was not significantly associated with risk of nonfatal or fatal stroke or transient ischemic attack [B]. Results of the first clinical trial of HRT in women with prior stroke indicate no reduction in the risk for recurrent stroke and death and suggest increased risk for more severe strokes in the first few months after initiation of HRT [B].²

7.3 Peripheral Vascular Disease

Peripheral vascular disease occurs fairly commonly in women, and, as in all atherothrombotic CVD incidence increases with age in women. Smoking is the most prevalent risk factor for peripheral vascular disease, as it is in men. Peripheral vascular disease carries with it an increased risk for CHD, which is not gender dependent.

- **Hormone replacement therapy.** The effect of HRT on peripheral vascular disease is unknown.

7.4 Venous Thromboembolism

Modifiable risk factors for venous thromboembolism include the presence of hemostatic disorders, immobilization, and perhaps obesity. Although most cases of venous thrombosis are not fatal, death from pulmonary embolism can occur, and postthrombotic syndrome occurs in as many as one-fourth of patients with deep venous thrombosis. Venous thromboembolism remains a major cause of morbidity and mortality after gynecologic surgery.

¹ Clarke S, Kelleher J, Lloyd-Jones H, et al. Transdermal hormone replacement therapy for secondary prevention of coronary artery disease in postmenopausal women. *Eur Heart J* 2000;21(Abstract Supplement):212.

² Viscoli CM, Brass LM, Kernan WN, et al. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001;345:1243–9.

- **Hormone replacement therapy:** Findings from recent observational studies and data from clinical trials show a consistent increase in risk for venous thromboembolic events in women taking estrogen compared with those that do not [A]. These studies indicate that there may be a fourfold increase in RR initially, with a persistent twofold increase in risk thereafter. The increased risk for venous thromboembolism was similar in women using an estrogen plus progestin [B]. Similar risk is associated with the SERM raloxifene.³

7.5 Pulmonary Disease

Estrogen may play a role in the pathophysiology of asthma. Observational studies suggest a positive dose response for use of CEEs and risk for asthma. Otherwise, there appears to be little impact of menopause or HRT on the pulmonary system, although further research is warranted.

8. OSTEOPOROSIS AND ORAL BONE LOSS: RISKS AND THERAPY

8.1 Osteoporosis

- Osteoporosis affects a large proportion of the population of elderly women throughout the world. More women than men are affected. The overall lifetime risk for fractures in women in the United States and most European countries is from 30 to 40 percent, but there is clear variability across cultures. Worldwide for women and men, about 1.26 million hip fractures occur each year, a number expected to double by 2025.
- Rates of osteoporosis and related bone fractures increase with age. Low bone mass at menopause can be due to insufficient bone acquisition during growth or bone loss during adulthood. Ovarian failure heralds dramatic

changes in skeletal homeostasis. Bone loss accelerates for a few years after natural menopause or oophorectomy, and continues at a lower rate for the remainder of life. The mechanism of how loss of estrogen at menopause contributes significantly to skeletal bone loss is not completely understood. Postmenopausal bone loss may be exacerbated by low levels of physical activity and poor nutrition, especially low calcium intake. Severe bone loss and fractures are not natural consequences of aging and can be prevented or substantially delayed.

- The principal method for making the diagnosis of osteoporosis is evaluation of the skeleton by using a noninvasive measurement of bone mineral density (BMD). Fracture risk is the most important determinant in patient selection for treatment or intervention for osteoporosis, although bone density is only one of many risk factors that contribute to risk for fracture. Although there has been major progress in methods for assessing risk for osteoporotic fracture, identifying individuals at greatest need for treatment remains a problem.

Osteoporosis affects a large proportion of the population of elderly women throughout the world.

8.1.1 Nonpharmacologic Interventions

Adequate nutrition—in particular, but not exclusively, from intake of calcium and vitamin D—and adequate physical activity are requisite preventive efforts against osteoporosis throughout life. Avoidance of tobacco use and moderation in alcohol intake are obvious.

- **Calcium.** Adequate calcium intake in older adults can retard bone loss and reduce risk for fracture. While it is recommended that calcium be obtained from the diet, not all

³ Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation [published erratum appears in JAMA 1999;282:2124]. JAMA 1999 281:2189-97.

individuals are able to increase calcium intake in this way. In such individuals, supplementation may be encouraged. In the United States, it is recommended that an average intake of about 1,200 mg of calcium per day should be achieved by adults ≥ 51 years of age [Dietary Reference Intake (DRI)].

- **Vitamin D.** Because it is inexpensive to provide vitamin D and because many of the controlled studies of calcium also used vitamin D supplementation, supplements of vitamin D are recommended for at-risk populations, especially those 65 years of age and older. For at-risk populations, 700 to 800 IU (international units) of vitamin D per day may be sufficient.

ERT maintains bone density and favorably influences markers of bone resorption.

- **Physical activity.** Bone density responses to increased physical activity in adults have been fairly modest. The type of exercise that promotes bone response may be different from the type recommended for aerobic fitness: Muscle building, weight bearing, resistance exercise is required to alter bone density [A]. Where not medically contraindicated, increased physical activity should be encouraged for all.

8.1.2 Pharmacologic Interventions

A decade ago estrogen and injectable calcitonin were the only available pharmacologic therapies for menopausal women with osteoporosis. Now there are new bone-specific drugs (e.g., bisphosphonates and parathyroid hormone (PTH)) and broad-spectrum drugs (e.g., SERMs) that combat osteoporosis and have potentially beneficial effects in other organ systems, as well as calcitonin delivered as an intranasal spray.

- **Hormone replacement therapy.** ERT maintains bone density and favorably influences markers of bone resorption [A].⁴ Long-term and continuing use of estrogen markedly reduces risk for fracture; discontinuation allows bone loss to occur, and fracture protection wanes [B].
- **Selective estrogen receptor modulators.** The SERM raloxifene exerts effects similar to those of estrogen in the skeleton and has been shown to prevent vertebral fractures [A].
- **Bisphosphonate therapy.** The first-generation bisphosphonate, etidronate, reduces vertebral but not nonvertebral fractures. Newer and more potent bisphosphonates have been shown to reduce risk for vertebral fracture by approximately 45 percent and to reduce risk for nonspine fracture to a lesser but clinically important degree [A].
- **Salmon calcitonin.** Salmon calcitonin can reduce resorption and help preserve bone mass. Vertebral fracture rates may be reduced [A/B]. Benefit in peripheral fracture risk has been suggested, but data are not conclusive.

Choosing among estrogen preparations, raloxifene, bisphosphonates, and calcitonin is challenging for individual patients. Considerations are the need for prevention versus treatment, the need for bone-specific versus broad-spectrum effects, patient acceptability and tolerance, and cost. The long-term effects of many of the newer agents (SERMs and bisphosphonates) are not known.

8.2 Oral Bone Loss

Oral bone, like the rest of the skeleton, comprises both trabecular and cortical bone and undergoes formation and resorption throughout the lifespan. When oral bone loss exceeds gain, it manifests as either loss of tooth-anchoring support or a diminu-

⁴ Torgerson DJ, Bell-Syer SE. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. *JAMA* 2001;285(22):2891–7.

tion of the remaining ridge in areas of partial or complete tooth loss.

The prevalence of oral bone loss is significant among adult populations worldwide and increases with age for both sexes. Oral bone loss and attendant tooth loss are associated with estrogen deficiency and osteoporosis [C]. As a consequence, women's experiences with postmenopausal osteopenia may affect the need for, and outcome of, a variety of periodontal and prosthetic procedures, including guided tissue regeneration and tooth implantation [D]. Furthermore, it is possible that oral examination and radiographic findings may be useful signs of extraoral bone diminution [C].

8.2.1 Interventions

Nonpharmacologic approaches to preserving oral bone include oral hygiene self-care behaviors, such as brushing and flossing; professional dental services, including oral examination, tooth scaling, and polishing; and smoking cessation. Calcium and vitamin D supplementation and pharmacologic therapies for osteoporosis, including HRT and bisphosphonates, may yield positive oral bone effects [C].

9. GYNECOLOGIC AND URINARY ASPECTS

Atrophic changes of the vulva and vagina are discussed in “Vulvovaginal Atrophic Symptoms” above (“Symptoms and the Menopause”). The present section highlights the assessment of uterine bleeding in older women, the occurrence of lower urinary tract atrophy, and abnormalities of pelvic floor and urinary tract.

9.1 Assessment of Uterine Bleeding

- During the menopausal transition, women request consultation for gynecologic evaluation when cycle irregularities start or when hot flashes and other complaints related to hypoenestrogenemia occur. The gynecologist may be the only medical contact for healthy women.

- Different patterns of uterine bleeding can be confusing when they occur in older women, and physicians must be alert to the possibility of genital tract pathology. Endometrial bleeding can be linked to endometrial pathology (atrophy, polyps, submucosal leiomyoma, hyperplasia, adenocarcinoma) or to general pathology, dysfunctional conditions, or drugs. Dysfunctional uterine bleeding is common between ages 40 and 50 years. The associated endometrial histology is highly variable. In some patients with bleeding, the endometrial histologic findings appear out of phase with endocrine events. In many, the endometrium will be hyperplastic and may be secretory until the year before menopause. In postmenopausal women, endometrial atrophy is the most common histologic finding.

- Cancer is not the most common cause of abnormal bleeding in perimenopausal women, but abnormal uterine bleeding occurring during perimenopause should be considered secondary to malignancy until proven otherwise.

The most important risk factors for endometrial cancer are obesity and menopausal use of unopposed estrogen, even at low dosages. See “HRT, Related Therapies, and Cancer Epidemiology” below, for a discussion of HRT and risk for endometrial cancer. Endometrial hyperplasia is a premalignant lesion, particularly when atypia is present. Endometrial hyperplasia but not atypia can be reversed by the administration of progestin.

- Bleeding during the estrogen-only phase of sequential combined HRT is much more likely to be associated with endometrial pathology than bleeding during the progestin phase. No

Different patterns of uterine bleeding can be confusing when they occur in older women, and physicians must be alert to the possibility of genital tract pathology.

available hormone formulation suits all women. Prolonged and/or heavy cyclical bleeding may be due to excess estrogen or insufficient

In observational studies, ERT reduces the frequency of urinary tract infections in the postmenopausal years.

progestin in the sequential formulation or to endometrial pathology. Breakthrough bleeding is associated with a hyperplastic endometrium but may also occur with an atrophic endometrium. Continuous administration of progestins with estrogens has been suggested to prevent the cyclical withdrawal bleeding associated with hormone regimens. A high incidence of irregular bleeding episodes (50 percent) has been observed during the first year.

- Transvaginal ultrasonographic measurement of endometrial thickness provides a noninvasive clinical indicator of endometrial status. Endometrial thickness < 4 mm usually corresponds to histologically atrophic endometrium; thickness greater than 4 to 7 mm correlates with increased incidence of endometrial pathology in postmenopausal women. The exact level is uncertain in women receiving HRT whose endometrium is often thicker than in untreated postmenopausal women. Present-day ultrasound scanning cannot replace histopathologic assessment of the endometrium in women receiving HRT. Management of bleeding during HRT includes observation, surgery, and specific changes in the treatment regimen.

9.2 Lower Genital and Urinary Tract Atrophy

- The epithelium of the inner layer of the vagina has high levels of ERs and undergoes progressive loss of cells during menopause due to estrogen depletion. Estrogen-dependent secretions decrease, leading to vaginal dryness and, in some women, vaginitis, vaginismus, and dyspareunia. Local estrogen proved as effective as systemic in treatment for vaginal dryness [A].
- Loss of glycogen-producing cells, a consequence

of vaginal and urethral atrophy, causes decreased production of lactic acid and an environment that favors vaginal and urethral infection. It is important to identify and treat patients with recurrent infections to prevent significant morbidity, which includes risk for renal impairment.

- In observational studies, ERT reduces the frequency of urinary tract infections in the postmenopausal years [D]. Its beneficial effects can partially be explained through its support of normal vaginal flora.

9.3 Pelvic Floor and Urinary Incontinence

- All four functional layers of the urethra—epithelium, connective tissue, vascular tissue, and muscle—are affected by estrogen status. Estrogen deficiency causes atrophic changes of the urethral epithelium and of the submucosa.
- Urinary incontinence (UI) is defined by the International Continence Society as involuntary loss of urine that is objectively demonstrable and is a social or hygienic problem.
- The relationship between menopause and UI is unknown and not well studied. Limited data are available to support the hypothesis that menopause is a major risk factor for incontinence, especially for stress and urge incontinence.
- Established UI can usually be divided as follows: stress incontinence, which occurs in the absence of detrusor activity; urge incontinence, when detrusor muscle contracts during the filling phase of the bladder; mixed incontinence, which is a combination of both stress and urge incontinence; and overflow incontinence, which is the result of bladder obstruction or injury. Other factors that can cause UI include decreased mobility, cognitive impairment, or medications.
- Evaluation and treatment for incontinence is dependent on the type of incontinence and the person's age, medical history, and desire for therapy.

9.3.1 Interventions

- In many cases, urine leakage can be prevented or improved by improving pelvic muscle tone through different kinds of exercises. Pelvic floor exercises (including Kegel exercises), vaginal weight training, and pelvic floor electrical stimulation significantly reduce incontinence in RCTs [A].
- Behavioral therapies can help patients regain control of bladder function. *Bladder training* teaches people to resist the urge to void and gradually expand the intervals between voiding. *Toilet assistance* uses routine or scheduled toileting, habit training schedules, and prompted voiding to empty the bladder regularly to prevent leaking.
- Pharmacological therapies for the treatment of UI vary accordingly to the kind of incontinence that needs to be treated.
 - **Muscarinic receptor antagonists.** Both tolterodine tartrate and oxybutynine significantly increased volume-voided/micturition and decreased micturition and incontinence episodes per 24 hours compared to placebo, but tolterodine only was significantly better than placebo in reducing micturition frequency [A].
 - **Hormone replacement therapy.** Uncontrolled trials showed subjective improvement of incontinence upon estrogen treatment, while no objective improvement in measures of urine loss was found in RCTs [A]. HERS found HRT to be associated with worsening of stress UI [A]. By reducing potential afferent stimuli from the bladder, such as lower urinary tract infections, estrogen may benefit urge incontinence [C].
 - **Bulking injections.** Periurethral injection of collagen in women with genuine stress incontinence and intrinsic sphincter deficiency has a low short-term cure rate and has not been shown to improve stress incontinence long-term [A].

- **Surgical treatment.** This intervention can be very effective in improving or curing stress incontinence.

10. MENOPAUSAL THERAPIES AND CANCER

Experimental, clinical, and epidemiological data support an important role for reproductive hormones in the aetiology of some human cancers, including breast, endometrium, and ovary. Whereas for common adult cancers, such as lung and colon cancers, incidence rises continuously and progressively with age, the slope of increase slows around the time of menopause for most hormone-dependent cancers. Worldwide, breast cancer is by far the most frequent invasive cancer in women and the leading cause of cancer death in women, accounting for more than 300,000 deaths each year. Ovarian cancer adds another 100,000 deaths each year, and cancer of the corpus uteri adds 40,000. The issue of the effect of menopausal therapies on risk for cancer is a critical one.

10.1 Hormone Replacement Therapy

Most of the potential favourable and adverse effects of HRT on cancer risks are restricted to current users.

- **Breast cancer.** In observational studies, there is no appreciable association between less than 5 years of use of HRT and risk for breast cancer. Longer use is associated with a small but significant excess breast cancer risk for current users but not for former users. Combined HRT may be associated with higher breast cancer risk compared with unopposed estrogen.

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- **Endometrial cancer.** Estrogen use is strongly related to increased risk for endometrial cancer. When progestins are given for 10 days or more per cycle, combined HRT is not related to a major excess risk for endometrial cancer.
- **Ovarian cancer.** Results of observational studies of HRT and ovarian cancer have been inconsistent. Available findings include the possibility that HRT increases risk for cancer of the ovary.
- **Colorectal cancer.** Observational studies suggest that HRT may reduce risk for colorectal cancer. No clinical trial data are available.
- **Other cancers.** There is no consistent relationship between the use of HRT and liver cancer, other digestive neoplasms, or melanoma.

10.2 Selective Estrogen Receptor Modulators

Given the recognized adverse effects of HRT, much recent attention has focused on assessing alternative approaches to treating menopause, including use of tamoxifen and other SERMs. SERMs may offer many of the advantages of HRT while eliminating some of the disadvantages.

- **Breast cancer.** SERMs may reduce risk for breast cancer. Tamoxifen has been shown to reduce the risk for breast cancer by almost 50 percent. One clinical study of raloxifene showed a strikingly reduced risk.³ Further studies of tamoxifen and raloxifene are in progress.

11. NEUROLOGIC FUNCTION, MENTAL HEALTH, AND EYE

The CNS and eye are among the many tissues thought to be affected by hormonal changes around the time of menopause. In the brain and eye, as in other target organ systems, estrogen interacts with specific intranuclear receptors and putative membrane receptors to regulate intracellular processes. HRT with estrogen or other sex steroids has the potential to influence brain and eye functions.

Few clinical characteristics or diagnostic procedures identify subgroups of women who can benefit from HRT for the prevention or treatment of disorders of neurologic function, mental health, or the eye [D]. Despite a strong biologic rationale, clinical data are sparse. Thus, recommendations regarding HRT to prevent or ameliorate the disorders are necessarily limited.

11.1 Cognitive Decline

Memory and other cognitive abilities change over time during adult life. Changes that represent «usual» or «normal» accompaniments of aging are not viewed as pathologic. Modest cognitive decrements initially detectable in middle age are accentuated at elderly age. Many studies suggest that sex hormones influence brain function throughout life, but there is little evidence that menopause per se initiates cognitive deterioration, and serum estrogen concentrations in postmenopausal women do not appear to be closely related to cognitive skills.

- **Hormone replacement therapy.** ERT may help preserve specific cognitive skills (e.g., verbal memory) immediately after induced menopause [B]. Clinical trial data of cognitive function with HRT during normal aging are limited and inconsistent [C].

11.2 Alzheimer's Disease and Other Neurologic Disorders

A number of neurologic conditions are associated with aging.

- **Hormone replacement therapy**
 - Alzheimer's disease. HRT begun after menopause may reduce risk of Alzheimer's disease [C]. In contrast, ERT begun after the onset of dementia does not improve Alzheimer symptoms [B].
 - Stroke. HRT does not appear to modify substantially the risk of stroke in older healthy women [A].
 - Other neurologic disorders. For many neurologic disorders, including epilepsy, migraine headache, multiple sclerosis, and

Parkinson's disease, no overall positive or negative impact of menopause or HRT on neurologic symptoms or disability has been described [C].

- Sleep disorders. Some sleep disturbances occurring during the climacteric may benefit from HRT [C].

11.3 Mental Health

Women of all ages have higher rates of depression than men, and geriatric depression is a particularly important public health concern. Hot flushes and other climacteric symptoms clearly affect the quality of a woman's life. The menopausal transition does not appear to represent a time of heightened vulnerability to affective disorders.

- *Hormone replacement therapy*
 - Mood. Hormonal changes associated with menopause have little direct impact on mood [C]. Limited data from studies of women without clinical depression suggest a beneficial effect of estrogen on mood [B].

11.4 Eye

Increasing age is often accompanied by visual loss or blindness, and diminished visual acuity among older persons affects women more often than men. Some observational studies suggest the potential relevance of estrogen in eye disease.

- *Hormone replacement therapy*
 - Maculopathy, cataract, and dry eye. There is little evidence that HRT alters risk for certain types of age-related maculopathy, cataract, or dry eye [C].

12. FUTURE NEEDS

As life expectancy continues to increase, a challenge for the future will be to maintain and improve the quality of life in women as they age through better management of menopausal symptoms and health risks associated with menopause. Despite exciting new research in the field of menopause, including the availability of more

choices for intervention and major breakthroughs in the understanding of ER-mediated effects, much work remains to be done. The increasing number of postmenopausal women and their increasing longevity highlight the importance of women's health and well-being.

Key needs for the field of menopause in the near future are outlined in table 1–3.

Note:

The Women's Health Initiative, NHLBI, NIH, is referred to throughout this International Position Paper. As this document went to press, the NHLBI stopped an important component of the WHI on the basis of recommendations by the study's Data and Safety Monitoring Board (DSMB), an independent advisory committee. The reasons for stopping this major clinical trial of estrogen plus progestin early were due to an increased risk of invasive breast cancer as well as increases in coronary heart disease, stroke, and pulmonary embolism in participants on estrogen plus progestin compared to women taking placebo pills. There were noteworthy benefits of estrogen plus progestin, including fewer cases of hip fractures and colon cancer, but on balance the harm was greater than the benefits. The study, which was scheduled to run until 2005, was stopped after an average follow-up of 5.2 years. However, because the balance of risks and benefits of estrogen alone is still uncertain, the DSMB recommended that that component of the WHI be continued unchanged.

Because of the importance of the information from the estrogen plus progestin study, the results were released early in an expedited article on July 9, 2002 on the JAMA Website. Links to the JAMA article and a related editorial, can be found at <http://www.nhlbi.nih.gov/whi/hrtupd/>.

Limited data from studies of women without clinical depression suggest a beneficial effect of estrogen on mood.

TABLE 1–3

Women’s Health and Menopause: Future Needs

<p>Menopause and Aging</p> <ul style="list-style-type: none">• Conduct more research on the biologic and psychosocial processes of menopause.• Conduct additional longitudinal studies using prospective observational designs and large cohorts on the natural history of menopause representing women from a broad array of racial/ethnic and socioeconomic backgrounds.• Undertake additional menstrual diary research with concurrent hormone measures, to establish biomarkers of women’s proximity to menopause.• Undertake additional research on fertility and contraception in the perimenopause.• Further understanding is needed about the reciprocal influences of lifestyle, decision to use HRT, and quality of life.• Providing women and their families with balanced information about menopause, fostering positive attitudes towards aging and menopause, and encouraging healthy lifestyles may improve their health and quality of life related to menopause.
<p>Symptoms and the Menopause</p> <ul style="list-style-type: none">• Better document the natural menopausal transition through prospective investigations to distinguish menopause-related changes from those of aging or disease.• Conduct questionnaire studies validating phytoestrogen intake against metabolic measures of metabolites in different cultural settings.• Conduct a larger RCT of phytoestrogen supplementation, including metabolic measures of metabolite levels.
<p>Sociocultural Issues</p> <ul style="list-style-type: none">• Undertake better controlled population-based studies using standardized instruments adapted to the culture studied.• Develop an interactive psycho-bio-cultural model of menopause.• Disseminate research results within cultures under study, so that women can make their own decisions about the need for and choice of interventions and treatment strategies.• Conduct more interdisciplinary research for a better understanding of interactive factors.
<p>Physiological Role of Estrogen and Estrogen Receptors and Pharmacologic Modulation of Estrogen Receptor Activity</p> <ul style="list-style-type: none">• Further characterize a possible antiproliferative role of ERβ in the uterus and mammary gland.• Determine the physiologic functions of ERβ in the ovary (role in polycystic ovarian syndrome?), bladder, urethra, bone, cardiovascular system, immune system, and CNS.• Develop ERα- and ERβ-specific agonists and antagonists for experimental and therapeutic purposes.• Attain different profiles of action for exogenous estradiol through use of different formulations.• Obtain higher specificity of action by identification of new target molecules involved in gene transcription.• Increase knowledge of the mechanisms involved in ER activation through membrane receptors to develop new pharmacologic compounds acting along these pathways.

TABLE 1–3 (continued)

<p>Sexuality</p> <ul style="list-style-type: none"> • Improve understanding of the natural hormone changes that occur with aging and menopause, and of the roles of endogenous estrogens and androgens in women’s sexuality. • Develop standardized methods to measure libido in women. • Better define the determinants of sexual health, including sexual desire and arousal, in postmenopausal women. • Increase knowledge about the effects of medications on female sexuality in postmenopause, including the role of therapeutic hormonal and nonhormonal agents in the treatment of sexual dysfunction. • Improve the transmission of information to postmenopausal women about sexual health.
<p>Cardiovascular and Pulmonary Disease</p> <ul style="list-style-type: none"> • Conduct urgently needed randomized controlled clinical trials to investigate the potential benefits and risks of different hormone preparations in women with and without prior CHD. • Investigate low dosages of oral estrogen, nonoral preparations, SERMs, and androgens in randomized trials with clinical outcomes. • Except for asthma, very little data exist on the effect of menopause or HRT on the respiratory system, and investigation of the effects on important disease entities should be considered.
<p>Osteoporosis and Oral Bone Loss: Risks and Therapy</p> <ul style="list-style-type: none"> • Develop noninvasive tools to measure bone quality or bone strength inexpensively. • Develop pharmacologic agents that will stimulate bone formation and restore lost bone. All currently approved drugs are antiresorptive. • Develop new pharmacologic agents for osteoporosis that are bone-specific and that can be used indefinitely. • Improve knowledge of the association between oral bone and the rest of the skeleton, in particular as related to therapeutic benefit.
<p>Gynecologic and Urinary Aspects</p> <ul style="list-style-type: none"> • Obtain additional data on the determinants of endometrial function and the specific effects of ovarian hormones on skin and different urogenital mucosae. • Develop new ERα and ERβ agonists and antagonists as well as new progestins. • Develop sensitive methods for early diagnosis at the molecular level of estrogen defects in various tissues. • Develop noninvasive methods of endometrial testing. • Improve knowledge of the relationship between HRT and the pelvic floor, including UI. • Develop reliable, easy-to-use diagnostic indexes for pelvic floor and urinary syndromes. • Develop new pharmacologic agents for the treatment of UI. • Design clinical trials to properly assess the relationship between SERMs and pelvic organ prolapse.

TABLE 1–3 (continued)

Menopausal Replacement Therapies and Cancer Epidemiology

- Further quantify the breast cancer risk of estrogen and estrogen-progestin regimens.
- Improve understanding of the relation between the use of HRT and risk for breast cancer according to age.
- Further investigate the (potentially favorable) biologic effects of HRT on the biologic characteristics of breast tumors.
- Undertake additional studies on the use of HRT in women with a diagnosis of breast cancer.
- Better quantify risk for endometrial cancer with combined HRT.
- Obtain additional data on the use of HRT and risks for cancers of the ovary, colon and rectum, lung, liver, and melanoma.
- Conduct additional research regarding cancer risks of the use of tamoxifen and other SERMs, as well as so-called natural therapies for postmenopause.
- Conduct RCTs to obtain data for the effects of SERMs on risks of various cancers.

Neurologic Function, Mental Health, and the Eye

- Explore the possibility that SERMs may act as estrogen antagonists as well as agonists in the brain or eye.
- Conduct cohort studies from representative populations and randomized controlled clinical trials to assess potential hormonal effects on age-associated cognitive decline, risk for Alzheimer’s disease and vascular dementia, mood, macular degeneration, and other disorders of neurologic function, mental health, and eye.
- Evaluate the effectiveness of combination replacement therapy with estrogen plus a cholinomimetic drug in RCTs for women with Alzheimer’s disease.
- Evaluate in RCTs the potential effects of HRT on primary prevention of Parkinson’s disease and on symptoms of Parkinson’s disease.
- Determine in RCTs whether estrogen combined with antidepressants or antipsychotic drugs might enhance effects of these medications in depressive disorders and schizophrenia, respectively.
- Determine in long-term RCTs whether HRT might reduce incidence of age-associated maculopathy, cataract, or dry eye.
- If beneficial effects of HRT are confirmed, undertake basic and clinical research to define mechanisms of action, optimal choice, timing of therapy and duration of usage of estrogen or SERMs, and potential modifying effects of progestin cotherapy.